[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DEFENSE ACADEMY]

A New Barbituric Acid Synthesis in Liquid Ammonia-Alkali Hydroxide. II.[1] Condensation of Malonamide Derivatives with Ethyl Carbonate

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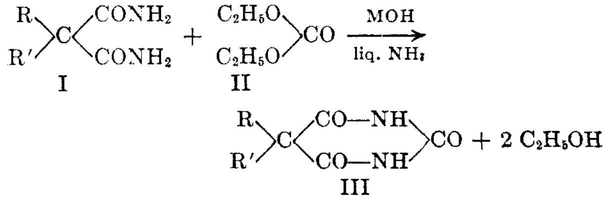
A new synthesis of barbituric acid derivatives has been devised. It was found that ethyl carbonate could be condensed readily with malonamide or its *C*-alkylated derivatives by using sodium hydroxide as the condensing agent in liquid ammonia. The effect on yield of variations in the reaction conditions was also studied.

The *C*-alkyl- and *C, C*-dialkyl-malonamides required in this investigation were successfully prepared by the alkylation of malonamide using sodium hydroxide in liquid ammonia. Six alkylated malonamides, two of these new, were prepared in excellent yields by this method.

A number of barbituric acid syntheses have been described in the literature. For example, malonic acid, as well as *C*-substituted malonic acids, have been condensed with urea. Urea has also been treated with malonyl and substituted malonyl chlorides. In addition malonamide has been treated with phosgene and *C,C*-dialkylmalonamides have been condensed with alkyl or phenyl carbonate. However, by far the most common procedure used in preparing barbituric acids is that based on the method of Michael,[2] namely, the condensation of urea with the appropriate diethyl malonate in the presence of sodium ethoxide in anhydrous alcohol. This is the method which has been generally adopted for the industrial production of barbituric acids and also represents the most common laboratory preparative procedure.

In a recent paper[1] we outlined a modification of the usual barbituric acid synthesis which used an alkali hydroxide as the condensing agent and liquid ammonia as the solvent. According to this procedure the diethyl dialkylmalonate, urea and an alkali hydroxide were dissolved or suspended in liquid ammonia and the mixture well agitated for about an hour in a pressure flask at room temperature. Dialkylbarbituric acids were produced in 50–60% yield. However, when diethyl malonate or monoalkylated diethyl malonates were tried none of the desired barbituric acids could be isolated.

The present investigation is concerned chiefly with still another approach to barbituric acid synthesis. We have now found that malonamides (I) condense readily with ethyl carbonate (II) in liquid ammonia in the presence of an alkali hydroxide or alkali amide. The reaction appears to be quite general, giving good yields of barbituric acids (III) with malonamide, *C*-alkylmalonamides or *C,C*-dialkylmalonamides. The yields obtained for six representative barbituric acids are shown in Table I. Also listed are the results of a study comparing the effect of various alkaline condensing agents on these yields. It will be noted that sodium hydroxide gave the most uniformly good results of any of the condensing agents used. *C,C*-Dialkylmalonamides have been condensed with alkyl or phenyl carbonate in the presence of alkali alcoholate in alcohol,[3] and also of alkali metal, alkali alcoholate or alkali amide without solvent.[4] The using of malonamide or *C*-alkylmalonamide in the reactions have never been described.



Where R, R′ = H, alkyl, allyl, etc.

The *C*-alkyl and *C,C*-dialkylmalonamides used in the present investigation were prepared according to a new method recently described by Asami and Shimo.[5] According to this procedure malonamide was alkylated using an alkali hydroxide in liquid ammonia at room temperature in a pressure flask. In the present work some improvements have been made in the synthesis of dialkylmalonamides, especially in the case of single step diallylation. It was found that this reaction was best carried out at atmospheric pressure and yielded more than 80% of diallylmalonamide from malonamide and two molar equivalents each of allyl bromide and sodium hydroxide in liquid ammonia. On the other hand, when the reaction was run under pressure at room temperature none of the desired diallyl derivative was obtained.

EXPERIMENTAL

Reagents. Malonamide was obtained by the ammonolysis of ethyl malonate in liquid ammonia[6]; m.p. 167–168.5°.

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(1) For the first paper in this series see K. Shimo and S. Wakamatsu, *J. Chem. Soc. Japan (Ind. Chem. Sect.)*, **60,** 1141 (1957).

(2) A. Michael, *J. prakt. Chem.*, (2) **35,** 449 (1887).

(3) Friedr. Bayer & Co., German Patent **163,136,** *Chem. Zentr.* **1905** II, 1141.

(4) Friedr. Bayer & Co., German Patent **168,406,** *Chem. Zentr.*, **1906** I, 1200.

(5) R. Asami and K. Shimo, *J. Chem. Soc. Japan (Ind. Chem. Sect.)*, **60,** 1034 (1957).

TABLE I

SYNTHESIS OF BARBITURIC ACIDS BY CONDENSATION OF MALONAMIDES WITH ETHYL CARBONATE IN LIQUID AMMONIA

$RR'C(CONH_2)_2$ R-	R'-	Condensing Agent[a]	Hours Shaken[b]	Product Barbituric Acid	Yield,[c] %	Malonamide Recovered[d]
H	H	NaOH	3		56	..
H	H	KOH	3,5		56	..
H	H	KNH_2	3		47	..
H	Ethyl	NaOH	1	Ethyl-	44	..
H	Ethyl	$NaNH_2$	1	Ethyl-	38	..
H	Ethyl	KNH_2	1	Ethyl-	36	
H	*i*-Amyl	NaOH	0,5	*i*-Amyl-	78(100)	22
H	*i*-Amyl	KOH	3	*i*-Amyl-	66(80)	17
H	*i*-Amyl	KNH_2	3	*i*-Amyl-	51(66)	22
Ethyl	Ethyl	NaOH	3	Diethyl-	35(77)	54
Ethyl	Ethyl	KOH	3	Diethyl-	14(47)	70
Ethyl	Ethyl	$NaNH_2$	4	Diethyl-	27(68)	69
Allyl	Allyl	NaOH	3	Diallyl-	82(95)	14
Allyl	Allyl	KOH	3	Diallyl-	65(93)	39
Allyl	Allyl	$NaNH_2$	3	Diallyl-	55(98)	44
Ethyl	*i*-Amyl	NaOH	5	Ethyl *i*-Amyl	40(100)	69
Ethyl	*i*-Amyl	KOH	5	Ethyl *i*-Amyl	4(100)	96
Ethyl	*i*-Amyl	$NaNH_2$	5	Ethyl *i*-Amyl	29(100)	70

[a] Approximately two molar equivalents of alkaline condensing agent were used per mole of $RR'C(CONH_2)_2$. When the ratio was either greater or less, yields were lowered appreciably. [b] The reaction mixtures were shaken continually at room temperatures for the period of time specified. Apparently the time element was not critical for periods ranging from 0.5 to 5 hours did not affect the yields significantly. [c] Yields based on the starting malonamides. Parenthesized figures indicate the yields calculated on the basis of the actual malonamide consumed. [d] Based on starting malonamides.

The commercially available ethyl carbonate was used; b.p. 124–126°. Sodium and potassium hydroxides were the commercial granulated products; purity, evaluated by the neutralization method, 93% and 87% respectively. The liquid ammonia was the commercial product once distilled in a bomb.

Syntheses of malonamide derivatives. Essentially two methods of alkylation were employed; (I) the use of a pressure vessel at room temperature and (II) the reaction at atmospheric pressure at the temperature of liquid ammonia (−33°). These are illustrated by the preparation of ethylmalonamide (Method I) and diethylmalonamide (Method II).

2-Ethylmalonamide (Method I). Malonamide (5.1 g.) (0.05 mole), 2.2 g. (approx. 0.05 mole) of sodium hydroxide and about 50 cc. of liquid ammonia were placed in a glass pressure vessel (Fig. 1). The mixture was shaken for 0.5 to 1 hr. at room temperature until the metallation was complete as indicated by the disappearance of the solid sodium hydroxide. To the mixture was then added 6 g. (0.055 mole) of ethyl bromide and the shaking continued for 1 to 2 hr. After evaporation of the ammonia the remaining solids were washed with cold water; yield, 4.6 g. (71%) of 2-ethylmalonamide; m.p. 209.2–211.5°. Conrad and Schulze[7] prepared this compound in 40% yield by the alkylation of malonamide using ethyl iodide as the alkylating agent and sodium methoxide as the condensing agent. We have almost doubled the yield by our new variation of this synthesis.

Fig. 1. Reaction vessel

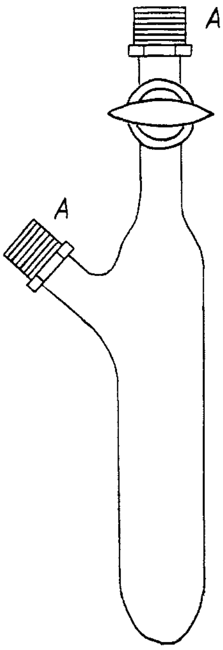
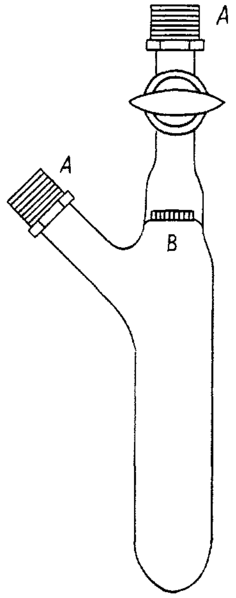


Fig. 2. Reaction vessel with glass filter



A. Stainless steel joint. B. Glass filter

2,2-Diethylmalonamide (Method II). In a well cooled (below −33°) one-liter three-necked flask provided with an efficient mercury sealed stirrer and a Dewar reflux condenser, protected by a soda-lime tube, were placed about 350 cc. of liquid ammonia and 11 g. (0.2 mole) of potassium amide.[8] While stirring vigorously, 26 g. (0.2 mole) of ethylmalonamide was added which formed potassioethylmalonamide. This was followed by the dropwise addition of 24 g. (0.22 mole) of ethyl bromide over the period of an hour. After an additional two hours of stirring the ammonia was evaporated and the remaining solids washed with water and then recrystallized from water; yield 21.2 g. (67%) of 2,2-diethylmalonamide which melted at 218–219.5°. This com-

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(6) K. Shimo and R. Asami, *J. Chem. Soc. Japan (Pure Chem. Sect.)*, **78**, 800 (1957), reported that a 97% yield of malonamide resulted by allowing a mixture of ethyl malonate and liquid ammonia (1:5.7 molar ratio) to stand at room temperature for four days. In the present work we added 10% of ammonium chloride (on a molar basis as compared to ethyl malonate) as a catalyst and thereby completed the reaction within 24 hr.

(7) M. Conrad and A. Schulze, *Ber.*, **42**, 729 (1909).

(8) K. W. Greenlee and A. L. Henne, *Inorg. Syntheses*, **2**, 135 (1946).

pound has been prepared previously by the ammonolysis of 2,2-diethylmalonyl chloride[9] or diethyl 2,2-diethylmalonate.[10]

2-Isoamylmalonamide was prepared in 89% yield by Method I using isoamyl iodide as the alkylating agent; m.p. 219.5–220.5°, after recrystallization from dilute alcohol.

Anal. Calcd. for $C_8H_{16}N_2O_2$: C, 55.81; H, 9.30; N, 16.28. Found: C, 55.76; H, 9.23; N, 16.35.

Hoffman[11] reported a melting point of 210° for this compound which he prepared by the ammonolysis of the corresponding diethyl ester in a closed tube.

2-Allylmalonamide (Method II). A 65% yield was obtained from malonamide and allyl bromide using sodium hydroxide as the condensing agent. After recrystallization from alcohol the product melted at 167°.

Anal. Calcd. for $C_6H_{10}N_2O_2$: N, 19.72. Found: N, 20.15.

2,2-Diallylmalonamide. This compound was synthesized in 66% yield from allylmalonamide and allyl bromide (Method I). The crude product melted at 194–199°. Using Method II, with potassium amide as the condensing agent, the yield was increased to 90% and the melting point raised to 201–202°.

The introduction of both allyl groups in a single step was achieved in 81% yield (Method II) by starting with malonamide and using two molar equivalent each of allyl bromide and sodium hydroxide; m.p. 198–200.5° (crude product). Meyer[12] prepared this compound by the ammonolysis of the corresponding dimethyl ester.

2-Ethyl-2-isoamylmalonamide (*Method I*) was prepared in 55% yield from ethylmalonamide and isoamyl iodide using sodium hydroxide as the condensing agent. The yield increased to 75% when potassium amide (prepared in the reaction vessel indicated in Fig. 2)[13] was used. The product, after recrystallization from dilute alcohol, melted at 191–192.5°.

Anal. Calcd. for $C_{10}H_{20}N_2O_2$: C, 60.00; H, 10.00; N, 14.00. Found: C, 59.82; H, 10.09; N, 13.77.

Synthesis of barbituric acid derivatives. In general the best results were obtained when the reactants were used in the approximate ratio of one mole of the appropriate malonamide to 1.3 moles of ethyl carbonate and 2 moles of an alkali hydroxide[14] or alkali amide. The following two examples represent typical procedures.

Barbituric acid. In a glass pressure vessel were placed 1.28 g. (0.0125 mole) of malonamide, 2. g. (0.017 mole) of ethyl carbonate, 1.1 g. (0.025 mole) of sodium hydroxide and 10–25 ml. of liquid ammonia. The mixture was then shaken at room temperature. In a moment most of the sodium hydroxide had disappeared and a brown precipitate (sodium barbiturate) began to separate. After 3 hr. the ammonia was evaporated off and the product, along with the easily soluble unreacted malonamide, was extracted with water. Neutralization of the extract with 50% sulfuric acid gave fine crystals of barbituric acid; yield 0.9 g. (56%), m.p. 243–244° (crude product).

5,5-Diallylbarbituric acid. A mixture of 1.82 g. (0.01 mole) of 2,2-diallylmalonamide, 1.5 g. (0.0127 mole) of ethyl carbonate, 0.9 g. (0.02 mole) of sodium hydroxide and 25 cc. of liquid ammonia was placed in a glass pressure vessel. After shaking for about 0.5 hr. at room temperature the reaction was substantially complete. The reaction was allowed to shake for a total of 3 hr. and then the ammonia removed. The sodium salt of the reaction product was extracted with water. Since the unreacted 2,2-diallylmalonamide was practically water insoluble it could be quantitatively recovered. Neutralization of the aqueous extract with concentrated hydrochloric acid precipitated the fine crystals of 5,5-diallylbarbituric acid; yield, 1.7 g. (82% based on starting amide). After recrystallization from water it melted at 171°.

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(9) K. Böttcher, *Ber.*, **39**, 1596 (1906).

(10) B. Russell, *J. Am. Chem. Soc.*, **72**, 1853 (1950).

(11) P. Hoffman, *Ber.*, **23**, 1498 (1890).

(12) H. Meyer, *Monatsh.*, **27**, 1091 (1906).

(13) Potassium amide was readily prepared in the reaction vessel pictured in Fig. 2 and filtered directly into the reaction mixture through the fitted glass filter. However, sodium amide, being insoluble in ammonia, could not be prepared in the same fashion so was used directly as a suspension.

(14) The particle size of the commercial granulated product was reduced in a mortar before use.

[Contribution from the Westinghouse Research Laboratories]

Methylene Bridge Formation *via* Carbonium Ions in the Phenol-Formaldehyde Reaction

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Polyphenylmethylene structures are accepted as the principal component of polymers derived from the reaction of phenol and formaldehyde. The reaction between methylolphenol or halomethylphenol compounds and phenols to yield dihydroxydiphenylmethanes is interpreted in terms of a common, hydroxy substituted, benzyl cation intermediate. Experimental evidence in support of this intermediate is presented for the first time. In terms of this mechanism dibenzyl ether formation is viewed as a competing reaction which may predominate under special conditions. A case of preferential reaction between a hydroxybenzyl cation and an aromatic hydrocarbon is presented in which a phenol, although present, failed to react.

Reaction between phenol and formaldehyde to give resins is now well recognized to proceed stepwise.[1–5] There is first an addition of formaldehyde to phenol to give methylolphenols and second, a condensation of methylolphenol compounds with other phenols to form polymers joined predomi-

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(1) R. W. Martin, *Chemistry of Phenolic Resins*, J. Wiley and Sons, New York (1956).

(2) K. Hultzsch, *Chemie der Phenolharze*, Springer Verlag, Berlin (1950).

(3) J. F. Walker, *Formaldehyde*, 2nd ed., Chap. 12, Reinhold Corp., New York (1953).

(4) A. Zinke, *J. Appl. Chem.*, **1**, 257 (1951).

(5) M. Imoto, *J. Inst. Polytechn.*, *Osaka*, **2**, (2) Series C (1952).